WHAT'S NEW IN INTENSIVE CARE

Angiotensin II

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Angiotensin II (ANGII) is a vasoconstrictive eighth amino acid peptide, which increases blood pressure within a complex regulatory and counterregulatory system (Fig. 1). ANGII is the key molecule in the renin–angiotensin–aldosterone system (RAAS), which, together with catecholamines and vasopressin, maintains blood pressure and fluid homeostasis. These properties make angiotensin II a potential vasopressor drug for vasodilatory hypotension and/or shock in the intensive care unit (ICU). However, ANGII has not been commercially available until recently despite the fact that it had already been used safely in human studies for a long time [1]. In 2009, experimental work in Gram-negative septic sheep introduced the concept that septic acute kidney injury (AKI) may be partly due to efferent arteriolar vasodilatation and reported a marked beneficial effect of ANGII infusion on renal function [2]. This "rediscovery" of ANGII led to pilot work in humans [3] and then to the commercial development of an ANGII preparation (Giapreza®, La Jolla, San Diego, CA). This was followed by the Angiotensin II for the Treatment of High-Output Shock III (ATHOS-3) trial [4, 5]. This international multicentre double-blind, randomized controlled trial (DB RCT) aimed to obtain Federal Drug Administration (FDA) (with a cautionary note that it might increase the risk of thrombotic events) approval by demonstrating that, in catecholamine-refractory vasodilatory shock receiving > 0.2 µg/kg/min of norepinephrine equivalent, the administration of ANGII would increase mean arterial pressure (MAP) at 3 h of infusion by either 10 mmHg or to ≥ 75 mmHg without any increase in background vasopressors. ATHOS-3 compared 163 ANGII-treated patients to 158 placebo-treated patients. Most had septic shock. The trial demonstrated an eightfold greater odds ratio of achieving MAP target with ANGII, with success in 70% vs 23% of cases with placebo. The drug is now FDA-approved as a second-line vasopressor for the treatment of catecholamine-refractory vasodilatory shock. In the United States of America (USA), it has been used in thousands of patients. It is now also approved by the European Medicines Agency (EMA) for the same indication. In late 2020, it was used to support the circulation among hypotensive patients affected by coronavirus disease 2019 (COVID-19) [6] and has now also been used in cardiac surgery patients [7]. ANGII is now commercially available in Europe.
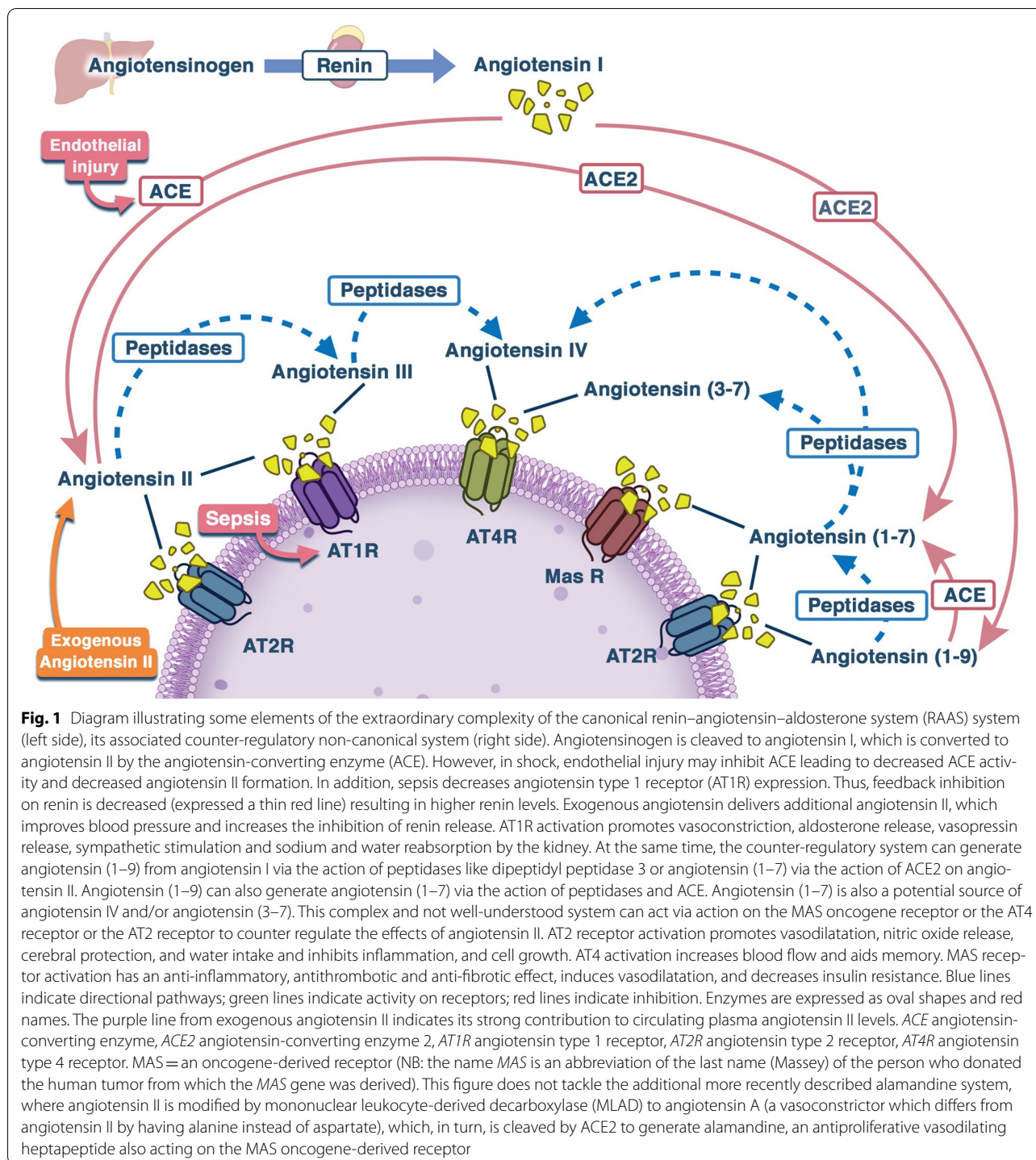
Post hoc subgroup analyses of the ATHOS-3 trial have provided additional data to show that patients on renal replacement therapy (RRT) at randomization had better rates of recovery to RRT independence at day seven and improved survival with ANGII [8] and that patients with an ANGI/II ratio below the median were significantly more likely to survive than those with values above the median (suggesting a degree of ANGII deficiency) [9]. A further ATHOS-3 post hoc study found that patients with a plasma renin concentration (PRC) above the median who received ANGII were significantly more likely to have a decrease in PRC and increased survival rates [10]. Thus, among patients with vasodilatory shock, there was significant heterogeneity of RAAS endotype. On current evidence, therefore, it appears reasonable to use ANGII as rescue vasopressor in vasodilatory shock as approved by the FDA and EMA, especially in those patients with elevated PRC.

More data have recently accrued about ANGII. A further secondary analysis of the ATHOS-3 trial data has suggested that ANG II initiation at lower catecholamine and/or vasopressin levels may lead to better survival [11]. In addition, experimental data have demonstrated that ANGII is a powerful opsonin, which facilitates bacterial clearance [12].

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Fig. 1 Diagram illustrating some elements of the extraordinary complexity of the canonical renin–angiotensin–aldosterone system (RAAS) system (left side), its associated counter-regulatory non-canonical system (right side). Angiotensinogen is cleaved to angiotensin I, which is converted to angiotensin II by the angiotensin-converting enzyme (ACE). However, in shock, endothelial injury may inhibit ACE leading to decreased ACE activity and decreased angiotensin II formation. In addition, sepsis decreases angiotensin type 1 receptor (AT1R) expression. Thus, feedback inhibition on renin is decreased (expressed a thin red line) resulting in higher renin levels. Exogenous angiotensin delivers additional angiotensin II, which improves blood pressure and increases the inhibition of renin release. AT1R activation promotes vasoconstriction, aldosterone release, vasopressin release, sympathetic stimulation and sodium and water reabsorption by the kidney. At the same time, the counter-regulatory system can generate angiotensin (1–9) from angiotensin I via the action of peptidases like dipeptidyl peptidase 3 or angiotensin (1–7) via the action of ACE2 on angiotensin II. Angiotensin (1–9) can also generate angiotensin (1–7) via the action of peptidases and ACE. Angiotensin (1–7) is also a potential source of angiotensin IV and/or angiotensin (3–7). This complex and not well-understood system can act via action on the MAS oncogene receptor or the AT4 receptor or the AT2 receptor to counter regulate the effects of angiotensin II. AT2 receptor activation promotes vasodilatation, nitric oxide release, cerebral protection, and water intake and inhibits inflammation, and cell growth. AT4 activation increases blood flow and aids memory. MAS receptor activation has an anti-inflammatory, antithrombotic and anti-fibrotic effect, induces vasodilatation, and decreases insulin resistance. Blue lines indicate directional pathways; green lines indicate activity on receptors; red lines indicate inhibition. Enzymes are expressed as oval shapes and red names. The purple line from exogenous angiotensin II indicates its strong contribution to circulating plasma angiotensin II levels. *ACE* angiotensin-converting enzyme, *ACE2* angiotensin-converting enzyme 2, *AT1R* angiotensin type 1 receptor, *AT2R* angiotensin type 2 receptor, *AT4R* angiotensin type 4 receptor. MAS = an oncogene-derived receptor (NB: the name *MAS* is an abbreviation of the last name (Massey) of the person who donated the human tumor from which the *MAS* gene was derived). This figure does not tackle the additional more recently described alamandine system, where angiotensin II is modified by mononuclear leukocyte-derived decarboxylase (MLAD) to angiotensin A (a vasoconstrictor which differs from angiotensin II by having alanine instead of aspartate), which, in turn, is cleaved by ACE2 to generate alamandine, an antiproliferative vasodilating heptapeptide also acting on the MAS oncogene-derived receptor

The use of ANGII as primary vasopressor agent in cardiac surgery was recently compared to norepinephrine in a pilot DB RCT involving 60 patients. In this feasibility trial, compared with norepinephrine, ANGII started before surgery and targeting a MAP of > 70 mmHg proved equally safe and effective as vasopressor. It also decreased the duration of ICU stay and, unlike norepinephrine, did not show an increase in PRC, thus increasing the aldosterone:PRC ratio [13, 14]. Moreover, pre-operative exposure to RAAS inhibitors increased PRC and a higher PRC was associated with greater norepinephrine, but not greater ANGII, dose to achieve

target MAP. In another pilot before-and-after study of critically ill vasopressor-dependent patients [15], ANGII appeared safe and effective, was associated with increased ICU survival, decreased troponin release and, in patients with pre-admission RAAS inhibitor exposure, a lower peak creatinine level to day seven. Prospective comparative controlled trials of ANGII, however, remain few and small so far and are summarized in supplemental Table 1.

In summary, current evidence supports the view that ANGII is a safe and physiologically effective vasopressor in catecholamine-refractory vasodilatory hypotension and/or shock. However, more studies are needed to better understand the timing, patient selection, and duration of ANGII therapy and its use in combination with other agents to deliver effective, safe, multifaceted, and balanced vasopressor therapy. In this regard, a RCT has just been completed which compared ANGII to norepinephrine in vasoplegic cardiac surgery patients with a postoperative PRC increase (NCT05199492). Moreover, another RCT comparing ANGII to norepinephrine as primary vasopressor in vasodilatory hypotension (ACTRN1262100104382) is currently recruiting. Finally, a third RCT comparing ANGII to norepinephrine in higher risk cardiac surgery (ACTRN12623000848606p) in due to start in early 2024.

Knowns and unknowns and future directions

We currently have limited evidence to select a specific population beyond refractory vasodilatory shock, where ANGII may be of greatest benefit. The use of renin to guide patient selection seems logical and is supported by retrospective data but needs to be confirmed prospectively. The preferential use of ANGII in vasodilatory shock patients with stage-3 AKI is similarly supported by retrospective data but needs to be confirmed by future AKI-focused RCTs. The safety and efficacy of ANGII as primary or secondary (instead of vasopressin) vasopressor in different types of vasoplegia is being investigated and needs to be tested in different contexts. Moreover, the interaction between recent exposure to RAAS inhibiting drugs and ANGII therapy appears important but needs to be clarified in larger prospective cohorts and trials. Finally, the clinical significance of the non-canonical ANGII counter-regulatory system (Fig. 1) in vasodilatory shock is essentially unexplored and requires dedicated studies with or without ANGII.

Supplementary Information

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